

**WE CLAIM**

1. A method of detecting whether a candidate polypeptide including a target epitope is in i) a wildtype conformation or ii) a non-wildtype conformation, comprising:

contacting the polypeptide with a blocking agent that selectively blocks accessible target epitope, wherein in the wildtype conformation, the target epitope is accessible and reacts with the blocking agent, and wherein in the non-wildtype conformation, the target epitope is inaccessible because the candidate polypeptide is aggregated and the target epitope cannot react with the blocking agent;

removing unreacted blocking agent from contact with the polypeptide;

modifying the candidate polypeptide to convert any inaccessible target epitope to accessible target epitope; and

contacting the polypeptide with a detection agent that binds selectively to the target epitope that was converted from inaccessible target epitope to accessible target epitope, wherein binding between detection agent and converted target epitope indicates that the candidate polypeptide was in a non-wildtype conformation and wherein lack of binding between the detection agent and the target epitope indicates that the polypeptide was in a wild type conformation.

2. The method of claim 1, wherein the candidate polypeptide comprises prion protein, the wild type conformation comprises the conformation of wild type prion protein and the non-wildtype conformation comprises the conformation of  $\text{PrP}^{\text{Sc}}$ .

3. The method of claim 1, wherein the candidate polypeptide comprises beta-amyloid polypeptide, tau protein or APP protein.

4. The method of claim 1, wherein the candidate polypeptide comprises SOD1.
5. The method of claim 1, wherein the candidate polypeptide comprises alpha-synuclein.
6. The method of claim 1 wherein the candidate polypeptide comprises huntingtin protein.
7. The method of claim 1, wherein the candidate polypeptide comprises p53.
8. The method of claim 1, wherein the candidate polypeptide comprises islet amyloid polypeptide or resistin.
9. The method of any one of claims 1-8, wherein the blocking agent is selected from the group consisting of peroxynitrite, hydrogen peroxide, methylene compounds, succinic anhydride, epoxides, diethyl pyrocarbonate, 4-hydroxynonenal (4HNE) and diazirine.
10. The method of any one of claims 1-9, wherein the polypeptide is modified by denaturing the polypeptide.
11. The method of any one of claims 1-10, wherein the polypeptide is denatured by heat and/or detergent and/or chaotropic agents.
12. The method of any one of claims 1-11, wherein the polypeptide is modified by treatment with a disaggregation agent to disaggregate the polypeptide from the aggregated polypeptides.
13. The method of claim 12, wherein the disaggregation agent is selected from at least one of the group consisting of chaotropic agents, detergent and heat.
14. The method of claim 13, wherein the detergent comprises SDS.

15. The method of any one of claims 1-14, wherein the detection agent comprises an aptamer or an antibody.
16. The method of claim 15, wherein the aptamer or antibody is directed against a prion polypeptide epitope.
17. The method of claim 16, wherein the antibody comprises 6H4 or 3F4,
18. The method of claim 15, wherein the aptamer or antibody is directed against an amyloid beta epitope.
19. The method of claim 16, wherein the antibody comprises 6E10 or 4G8.
20. The method of any one of claims 1-19, wherein the non-wildtype conformation is indicative of a disease caused by protein aggregation.
21. The method of claim 20, wherein the disease comprises prion disease.
22. The method of claim 20, wherein the disease comprises BSE or CJD.
23. The method of claim 20, wherein the disease comprises Alzheimer's disease.
24. The method of claim 20, wherein the disease comprises Parkinson's disease or Lewy body disease.
25. The method of claim 20, wherein the disease comprises Huntington's disease.
26. The method of claim 20, wherein the disease comprises amyotrophic lateral sclerosis.
27. The method of claim 20, wherein the disease comprises cancer.

28. The method of claim 20, wherein the disease comprises diabetes.
28. The method of any one of claims 1-28, wherein prior to contacting the blocking agent with the candidate polypeptide, the candidate polypeptide is in a sample that is pretreated by one or more of the following methods: adsorption, precipitation, or centrifugation.
29. The method of any one of claims 1-28, wherein prior to contacting the blocking agent with the candidate polypeptide, the target epitope is mapped.
30. The method of any one of claims 1-28, wherein the polypeptide is in a postmortem or antemortem sample selected from the group of: CSF, serum, blood, urine, biopsy sample or brain tissue.
31. A kit for detecting whether a candidate polypeptide including a target epitope is in i) a wildtype conformation or ii) a non-wildtype conformation, comprising a detecting agent that recognizes the target epitope and instructions for at least one of i) mapping a target epitope, ii) contacting a candidate polypeptide with a blocking agent, and iii) contacting a candidate polypeptide with a detecting agent.
32. The kit of claim 31 wherein the detecting agent comprises an aptamer or an antibody.
33. The kit of claim 32 wherein the antibody comprises 6H4, 3F4, 6E10 or 4G8, optionally immobilized to a solid support.
34. The kit of any one of claims 31-33, further comprising buffers and reagents for ELISA, including sandwich ELISA, fluorescent ELISA.
35. The kit of any one of claims 31-34 further comprising a blocking agent.
36. The kit of any one of claims 31-35 further comprising a denaturing agent selected from at least one of the group of detergents and chaotropic agents.

37. The kit of any one of claims 31-36, further comprising a polypeptide standard.

38. The kit of claim 34, wherein the polypeptide standard comprises a recombinant disease protein or a recombinant protein that mimics a disease protein.

39. A method of detecting whether a candidate polypeptide that has been contacted with a blocking agent is i) a wildtype conformation or ii) a non-wildtype conformation, wherein the candidate polypeptide comprises at least one target epitope and, following contact with the blocking agent and removal of the blocking agent, the candidate polypeptide has been modified to convert any inaccessible target epitope to accessible target epitope, the method comprising:

contacting the polypeptide with a detection agent that binds selectively to the target epitope that was converted from inaccessible target epitope to accessible target epitope, wherein binding between detection agent and converted target epitope indicates that the candidate polypeptide was in a non-wildtype conformation and wherein lack of binding between the detection agent and the target epitope indicates that the polypeptide was in a wild type conformation.